PATENT
Docket No.: 1662/49502

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	SINGER ET AL.
SERIAL NO.	:	09/552,485
FILING DATE	:	April 18, 2000
FOR	:	NOVEL SYNTHESIS AND CRYSTALLIZATION OF PIPERAZINE RING-CONTAINING COMPOUNDS
GROUP ART UNIT	:	1624
EXAMINER	:	K. Habte

Address to:
Assistant Commissioner for Patents
Washington D.C. 20231

DECLARATION OF JUDITH ARONHIME UNDER 37 C.F.R. § 1.132

I, JUDITH ARONHIME, Ph.D., of Harav Maor Josef 5a, Rehovot Israel, having been warned that I must state the truth or be liable to the penalties prescribed by law for failure to do so, declare as follows:

1. I have worked for Teva Pharmaceutical Industries, Ltd. ("Teva") since January 1991. Since then I have been in charge of the solid state characterization laboratory at Teva. I received the Ph.D. degree from the Casali Institute of Applied Chemistry, the Hebrew University of Jerusalem in 1989. As head of the solid state characterization laboratory I have continued to study and use known techniques of solid state characterization and to use them to develop specific methods for the identification and quantification of compounds of interest. In our laboratory we have characterized the solid state properties of over 30 drugs and drug products. I supervise five coworkers. Teva has and continues to invest in state-of-the-art equipment to carry out these solid state characterizations at Teva's solid state characterization laboratory in Israel.

2. Unless otherwise stated, I have personal knowledge of the solid state characterization of the materials discussed below: I either carried out or supervised these characterizations.

3. I have read and understood the specification and claims of the above-captioned patent application entitled "Novel Synthesis and Crystallization of Piperazine Ring-containing Compounds".

4. I have read and understood the Office Action dated March 13, 2002. The Office Action alleges, *inter alia*, that the mirtazapine form disclosed in an article by Kaspersen et al. anticipates claims 29-43 of the present invention.

5. I have read and understood the disclosure of Kaspersen, particularly the process describing the preparation of mirtazapine and its characterization. Kaspersen's process for preparing mirtazapine does not include a drying step. The resulting product is described as colorless crystals having a melting point of 123.8-125.8 °C and IR peaks at 1585, 1565, 1460 and 1440 cm^{-1}.

6. I understand that Claude Singer (see attached Singer Declaration, Exhibit 1) conducted an experiment in which an adduct of mirtazapine and water was prepared according to Example 6 of the above-captioned application, which states, in relevant part, the following:

> Mirtazapine (20 g), obtained as in Examples 2 and 3, is suspended in 20 mL of ethanol and heated to reflux. At reflux, 40 mL of water is added dropwise to the solution over one hour followed by cooling to 10° C. The resulting filter cake is washed with a solution of water:ethanol (2:1) and dried at 60° C under a vacuum.

7. Various properties of the mirtazapine adduct obtained in the preceding paragraph were ascertained immediately before and after the drying step. These properties were % water, melting point, IR spectrum, and color. The following results were obtained.

	Before Drying	After Drying
water content (wt %)	3.2	0.2
melting point (°C)	115.7	115.7
IR peaks (cm^{-1})	1586 1568 1444	1587 1566 1467 1445
color	white to creamy	white to creamy

8. Based on the differences in properties described above, particularly melting point and IR, I conclude that the mirtazapine form described in Kaspersen is not an adduct of mirtazapine and water containing between 0.2 and 3.2% by weight water.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: _____ Signed _____

Judith Aronhime, Ph.D.